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Liver transplantation for deterioration in native liver function after portoenterostomy for biliary atresia in Japan: Short- versus long-term survivors☆,☆☆

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ABSTRACT

Purpose: We reviewed our post-Kasai portoenterostomy biliary atresia (BA) patients who required liver transplantation (LTx) for deterioration in native liver (NL) function to investigate mortality in relation to age at LTx.
Methods: BA patients indicated for LTx when less than 18 years old (U18; n = 17) and when 18 or older (18+; n = 13) were compared. All achieved jaundice clearance postoperatively (TBil ≤1.2 mg/dL (≈20 μmol/L)).
Results: In U18, living-donor (LD) LTxs were performed at a median of 6.1 years (range: 0.5–16.7; n = 14) and cadaveric (CD) LTxs at a median of 1.3 years (1.1–1.5; n = 3). In 18+, LDLTxs were performed at a median of 28 years (18–37; n = 8), and 1 case died from graft versus host disease. CDLTxs were indicated in 5, but 4 died at a median of 30 years (26–32), a mean of 1.4 years (0.7–1.8) after NL deterioration commenced. One case is awaiting CDLTx. At the time of review, all U18 and 7 LDLTx cases in 18+ were clinically stable. Mortality rates were 0% in U18 and 38% in 18+ (P = .006).
Conclusion: Our results highlight the extremely grave prognosis for long-term BA patients requiring LTx when 18 or older because of poor donor availability in Japan.
Level of evidence: Level III.

While Kasai portoenterostomy (KPE) is the initial procedure performed for biliary atresia (BA), it is not curative in the majority of BA patients because they will eventually develop end-stage liver disease requiring liver transplantation (LTx).

Indications for LTx in BA patients included failed KPE (i.e., no jaundice clearance: JC), recurrent cholangitis, progressive/sudden deterioration in native liver (NL) function, or progressive manifestations of portal hypertension [1]. Shinkai et al. [2] reported that episodes of cholangitis and gastrointestinal bleeding began to occur in 37% and 17% of adult (more than 20 years old) BA patients, respectively, and that 20% of adult BA patients either had died from liver failure or had been transplanted while in their 20s. There is no doubt of the absolute indication for LTx in BA patients who do not achieve JC after KPE or those who become persistently icteric owing to progressive portal hypertension or recurrent cholangitis after successful KPE (i.e., achieving JC initially), but BA patients with NL after successful KPE who are relatively stable clinically and non-icteric, but have episodes of cholangitis or signs of progressive portal hypertension, may also be indicated for LTx as a consequence of the natural history of BA which may be difficult for patients to appreciate while they are asymptomatic and stable. Unfortunately, NL function can deteriorate suddenly in non-icteric BA patients with no history of cholangitis after successful KPE so all post KPE patients should be aware of the potential need for LTx.

As more post-KPE BA patients survive, the number of patients who may require LTx is also increasing and LTx in long-term survivors with NL is most likely to be indicated for sudden deterioration in NL function after the age of 18. Therefore, the aim of this study was to investigate the mortality of post-KPE BA patients who required LTx and assess factors that might influence outcome/prognosis in relation to age at LTx. We compared long-term survivors who required LTx before they were 18 years old (U18) with those who required LTx when they were 18 or older (18+) to identify any trends.

Abbreviations: BA, Biliary atresia; LTx, Liver transplantation; LD, Living-donor; LDLTx, Living-donor liver transplantation; CD, Cadaveric-donor; CDLTx, Cadaveric-donor liver transplantation; NL, Native liver; JC, Jaundice clearance; JLTS, Japanese Liver Transplantation Society.

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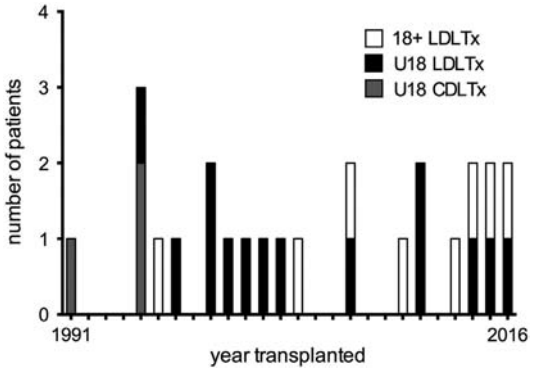

Fig. 1. Liver transplantations performed per year in our post-KPE BA patients. KPE: Kasai portoenterostomy. LDLTx: Living-donor liver transplantation. CDLTx: Cadaveric-donor liver transplantation.

1. Methods

We retrospectively reviewed all post-KPE BA patients indicated for LTx until December 31, 2016. KPE was performed at our institute between 1975 and 2014, and LTx has been available since 1991. Subjects were divided into two groups according to age at LTx; less than 18 years of age (U18 group) and 18 or older (18+ group). All subjects in this study achieved JC (defined as TBil ≤1.2 mg/dL) initially. We investigated the indications for LTx, age at LTx, type of donor: living (LD) or cadaveric (CD), and outcome.

Statistical analyses were performed using GraphPad Prism software version 6.0 (GraphPad Software). The differences in mortality were analyzed using the log-rank test. Statistical significance was defined as $P < .05$.

This study was approved by the Ethics Committee of Juntendo University School of Medicine and complies with the Helsinki Declaration of 1975 (revised 1983).

2. Results

We identified 30 BA patients who underwent KPE and were indicated for LTx by 31 December, 2016; U18 (n = 17) and 18+ (n = 13). All patients indicated for LTx without a suitable LD were registered on a waiting list for CDLTx (Fig. 1). There were 3 cases in U18 and 5 cases in 18+.

In U18, LDLTxs were performed in 14 patients at a median of 6.1 (range: 0.5–16.7) years and CDLTxs were performed in 3 patients at a median of 1.3 (1.1–1.5) years. All CDLTxs were performed prior to 1995, overseas, after a waiting period of less than 2 months. At the time of review, all U18 cases were clinically stable after a mean of 13.4 years follow-up (0.6–25.9) (Table 1). In 18+, LDLTxs were performed in 8 patients at a median of 28 (18–37) years. At the time of review, 7/8 were clinically stable after a mean of 6.7 (0.9–20.9) years.

LD demographics were distinctly different between the 2 groups. In U18, parents made up 13/14 or 93% of LD; in 18+, LDs were siblings (n = 3/8 or 37%), spouses (n = 2/8 or 25%), or parents (n = 3/8 or 37%). One LDLTx case in 18+ died from graft versus host disease soon after LTx. In contrast, 4/5 CDLTx cases died on the waiting list at a median of 30 (26–32) years after a mean of 1.4 (range: 0.7–1.8) years after onset of NL deterioration at a median of 29 years (24–32 years). Of these, 2/4 died from liver failure and 2/4 died from ruptured esophageal varices associated with severe coagulopathy. The remaining 37-year-old case has been on a waiting list for CDLTx for more than 6 months (Table 2).

At the time of review, 24/30 (U18: n = 17/17; 18+: n = 7/13) were alive, 5/30 had died (U18: n = 0/17; 18+: n = 5/13), and 1/30 was awaiting CDLTx. Mortality rates were 0/17 (0%) in U18 and 5/13 (38.5%) in 18+ (P = 0 .006) (Table 3). Because the 2 groups in our series are from different eras, we summarized when LTx was performed as a bar graph for each group per year (Fig. 1).

In U18, all 17 patients indicated for LTx had LTx and at the time of review, all 17 were alive and well. The LTx rate (performed:indicated) in U18 was 17:17 or 100% with a success rate of 17/17. The LTx rate in 18+ was 8:13 or 61% with a success rate of 7/13 or 54%. The success rate for LTx cases in 18+ was 7/8 (87%) and the failure rate was 1/8 (13%), while the failure rate in untransplanted 18+ cases was 4/5 (80%). Of note, success rate for LDLTx cases in U18 was 14/14 (100%) and in 18+ was 7/8 (87%) (P = N.S.).

3. Discussion

Our study found that BA patients who required LTx before the age of 18 because of early onset of progressive NL deterioration after successful LTx did better, based on anecdotal assessments of quality of life and morbidity/mortality rates, than long-term NL survivors who required LTx when 18 or older because of late onset of progressive NL deterioration or sudden onset of NL deterioration after a prolonged period of stability. Thus, LTx must be available as an option for the surgical treatment of BA because it may be the only real chance for a "cure", and certainly the only option once NL deterioration is severe. However, this is particularly poignant in Japan where LDLTx had to be developed because of a chronic scarcity of CDLTx [3]. According to the Japanese

Table 1
U18 patients.

Case	Sex	Type of LTx	Age at LTx (years)	Donor	Age at entry to WL (years)	Period since LTx (years)	Outcome
1	F	LD	8.7	Parent	-	21.2	Alive, well
2	F	LD	16.5	Parent	-	13.2	Alive, well
3	F	CD[a]	1.3	Cadaver[a]	1.1	25.9	Alive, well
4	F	LD	11.8	Parent	-	15.4	Alive, well
5	M	LD	9.0	Parent	-	17.1	Alive, well
6	F	CD[a]	1.5	Cadaver[a]	1.3	21.3	Alive, well
7	F	CD[a]	1.1	Cadaver[a]	0.9	21.4	Alive, well
8	F	LD	0.8	Parent	-	19.1	Alive, well
9	F	LD	5.0	Parent	-	14.1	Alive, well
10	F	LD	1.8	Parent	-	17.1	Alive, well
11	M	LD	1.3	Aunt	-	17.3	Alive, well
12	F	LD	9.4	Parent	-	9.0	Alive, well
13	M	LD	16.7	Parent	-	0.6	Alive, well
14	M	LD	0.6	Parent	-	5.4	Alive, well
15	F	LD	0.5	Parent	-	5.2	Alive, well
16	M	LD	2.8	Parent	-	2.3	Alive, well
17	M	LD	0.8	Parent	-	1.5	Alive, well

LTx: liver transplantation, LD: living-donor, CD: cadaveric-donor, WL: waiting list.
[a] Performed overseas.